part of #9

NEW DOCKET NO. INHA0012ICO/US (OLD DOCKET NO. 212345US22CONT)

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:
FELIX FRANKS ET AL : EXAMINER: RUSSEL

SERIAL NO. 09/939,689

FILED: AUGUST 28, 2001 : GROUP ART UNIT: 1653

FOR: STORAGE OF MATERIALS

37 CFR 1.175 REISSUE DECLARATION BY THE ASSIGNEE

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

I. **37 CFR 1.172 Declaration by the Assignee**

1. The written consent to this reissue application by the assignee owning an undivided interest in the patent is filed concurrently herewith. The reissue application does not seek to enlarge the scope of the claims of the original patent. The assignee has established their ownership interest in the patent by filing a submission in accordance with the provisions of 37 CFR 3.73(b).

II. **37 CFR 1.175**

A. **37 CFR 1.175(a)**

2. This declaration is executed in accordance with 37 CFR 1.68. Specifically, the undersigned has been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and willful false statements may jeopardize the validity of this application or any patent issuing thereon. All of the undersigned's statements based upon personal knowledge are true, and all of the undersigned's statements made on information and belief are believed to be true.

1. **37 CFR 1.63(a)(2)**

3. This declaration is directed to the specification for application serial No. 09/939,689 which is a continuation of application serial No. 09/270,791, which is an application to reissue the 5,098,893 patent to Franks et al.

2. **37 CFR 1.63(a)(3)**

4. There are two inventors.

5. The full name of the first inventor is Felix Franks. Felix Franks' residence, Post Office address is 25 The Fountains, 229 Ballards Lane, London N31NL, United Kingdom.. Felix Franks is a citizen of the United Kingdom.

6. The full name of the second inventor is Ross H. M. Hatley. Ross Hatley's residence, Post Office address is 47 Fen End, Willingham, Cambridge. Ross Hatley is a citizen of the United Kingdom.

3. **37 CFR 1.63(a)(4)**

7. Felix Franks and Ross Hatley are joint inventors of the inventions claimed.

4. **37 CFR 1.63(b)(i)**

8. I have reviewed and I understand the contents of the specification, including the claims, as proposed to be amended upon filing, and as proposed to be amended with a response being filed concurrently with this declaration.

5. **37 CFR 1.63(b)(2)**

9. I believe the named inventors to be the original and first inventors of the subject matter which is claimed and for which a patent is sought.

6. **37 CFR 1.63(b)(3)**

10. I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

7. **37 CFR 1.63(c)**

11. The foreign application is United Kingdom application No. 8903593 filed February 16, 1989. Priority is claimed from that application.

8. **37 CFR 1.63(d)**

12. This section is inapplicable.

9. **37 CFR 1.63(e)**

13. This section is inapplicable.

B. **37 CFR 1.175(a)(1)**

14. I believe the original patent to be wholly or partly inoperative or invalid by reason of the patentee claiming more or less than the patentee had the right to claim in the patent, and I rely upon the statement of the error in the originally filed parent reissue application No. 09/270,791 which is:

> In original claim 12, a method claim, with a phrase "and forming the resulting mixture into a glassy amorphous state" arguably encompasses removing water from the mixture by sublimation, also known as freeze drying.;

and the statement which is:

> The applicants failed to claim a process "of forming a composition which is storage-stable at 20° C, said composition comprising the steps of:
> (1) dissolving to form an aqueous solution
> (a) a carrier substance which is water-soluble or water-swellable and
> (b) at least one material to be stored;
> (2) evaporating liquid water from said solution to convert said solution into a composition in a glassy state;
> wherein said composition has the properties that it is storage-stable and exists in said glassy state when at 20° C;
> wherein said composition contains no more than 4 percent by weight of water;
> wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution when at 20° C;
> wherein said at least one material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any

of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said step of evaporating comprises heating the combined carrier substance and purified biologically active material to a temperature not exceeding 80° C."

C. **37 CFR 1.175(a)(2)**

15. All errors being corrected in the reissue application arose without any deceptive intention on the part of the applicant.

III. **37 CFR 1.175(b)**

16. Every error addressed by the claims filed with this declaration arose without any deceptive intention on the part of the applicant.

IV. **37 CFR 1.175(c)**

17. This section provides no additional requirements.

V. **37 CFR 1.175(d)**

18. This section is inapplicable.

IV. **Jurat**

19. I declare under penalty of perjury of the laws of the United States that the foregoing is true and correct.

_____ _____

Date

Felissa H. Cagan
Senior Director, Intellectual Property,
Inhale Therapeutic Systems, Inc.

of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said step of evaporating comprises heating the combined carrier substance and purified biologically active material to a temperature not exceeding 80° C."

C. **37 CFR 1.175(a)(2)**

15. All errors being corrected in the reissue application arose without any deceptive intention on the part of the applicant.

III. **37 CFR 1.175(b)**

16. Every error addressed by the claims filed with this declaration arose without any deceptive intention on the part of the applicant.

IV. **37 CFR 1.175(c)**

17. This section provides no additional requirements.

V. **37 CFR 1.175(d)**

18. This section is inapplicable.

IV. **Jurat**

19. I declare under penalty of perjury of the laws of the United States that the foregoing is true and correct.

October 3, 2002
Date

Felissa H. Cagan
Felissa H. Cagan
Senior Director, Intellectual Property,
Inhale Therapeutic Systems, Inc.

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Declaration 10/28/03

9849-0002-22 REISSUE

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: : EXAMINER: RUSSEL
FRANKS FELIX ET AL

SERIAL NO. 09/270,791 : GROUP ART UNIT: 1654

FILED: MARCH 17, 1999 :

FOR: STORAGE OF MATERIALS

SECOND DECLARATION UNDER 37 CFR 1.132 OF FELIX FRANKS

I. **Introduction**

1. A copy of my curriculum vitae is Attachment 20.

2. I am the first named inventor in United States patent No. 5,098,893 to Franks et al. entitled "Storage of Materials" which I refer to herein as the US patent.

II. **Facts Relating the Rejections of Claims for Lack of Written Description**

3. I have reviewed to office action mailed April 12, 2000 in this application to reissue the Franks et al. patent.

4. Counsel informs me that claim 17 now reads:

> --17. (Twice Amended) A composition which is storage-stable at 20°C, comprising:
> i) a carrier substance which is water-soluble or water-swellable and is in a glassy amorphous state;
> ii) at least one material to be stored, which is unstable in aqueous solution at room temperature of 20° C, and which is

dissolved in said amorphous carrier substance;

wherein said composition exists in a glassy state at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said at least one material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

said composition formed by a process comprising the steps:

dissolving said carrier substance and said at least one material with water; and

forming the carrier substance with said at least one material dissolved therein into said glassy state by evaporation of liquid water to produce a storage-stable composition that exists in said glassy state at 20°C.

A. **Claim 32**

5. Counsel informs me that claim 32 now reads:

32. (Once Amended) The composition according to claim 17, wherein said step of forming said carrier substance with said at least one material dissolved therein into a glassy state by evaporation of water comprises heating the combined carrier substance and purified biologically active material to at least 30° C and not exceeding 80° C .

6. This application teaches the "at the least 30° C and not exceeding 80° C" limitation in claim 32.

B. **Claim 34**

7. Counsel informs me that claim 34 now recites:

34. (Once Amended) The composition according to claim 17, wherein said step of forming said carrier substance with said at least one material dissolved therein into said glassy state by evaporation of water comprises maintaining a sub atmospheric pressure on the combined carrier substance and purified biologically active material while heating the combination to at least 30° C and not exceeding 80° C.

8. This application teaches the "at the least 30° C and not exceeding 80° C " limitation in claim 34.

C. **Claim 50**

9. Counsel informs me that claim 50 now reads:

50. (Not Amended) The composition according to claim 17 wherein said carrier substance comprises a ketohexose.

10. The compound referred to in the table in column 13 of the specification as sorbose is a ketohexose, it is an exemplary ketohexose, and one of ordinary skill in the art reading the specification in 1989 would have understood that the example in the specification of sorbose indicated that the invention was applicable with any ketohexose.

11. The ketohexoses consist of any monosaccharide composed of a six-carbon chain or ring and containing one ketone group. Froctose and sorbose are two members of the ketohexose family, which family is made up of a considerable number of structure land optical isomers. All ketohexoses have the generic formula $C_6(H_2O)_6$ and contain a C=O group.

12. The fact that the ketohexoses consist of any monosaccharide composed of a six-

carbon chain or ring and containing one ketone group was well known to one of ordinary skill in the art in 1989.[1]

13. In 1989, physical properties of the ketohexose sorbose, such as aqueous solubility and freezing point, were well known.[2] It was also well known that the molecular weight of all ketohexoses was identical. The thermo physical properties, such as Tg, were not well known, specifically, it was not well known in 1989 that the Tg of ketohexoses were significantly divergent.

14. Except for stereo optical activity properties, all ketohexose isomers have certain similar physical properties, such as melting point and molecular weight, and those facts were well known in the art in 1989.

15. In 1989, sorbose was considered by those of ordinary skill in the art to be exemplary of properties of other ketohexoses.[3]

16. Moreover, one of ordinary skill in the art in 1989 would have assumed that the glass forming properties of sorbose and fructose and their stereo isomers were similar to one

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[1]United States patent No. 4,455,333 to Hong et al. is attachment 31. The Hong et al. patent at column 5 lines 38-63 discloses a variety of hexoses, and identifies the ketohexoses psicose, fructose, sorbose, and tagatose and therefore, indicates that those ketohexoses were well known in the art as ketohexoses in 1989.

[2]See attachment 32, which is the title page, copyright page, and page 8568 of the Merck Index, which contains a description of the properties of sorbose. I have reviewed this attachment.

[3]Attachment 33 is United States patent No. 4,421,778 to Kahn et al. See the Kahn et al. patent at column 5 lines 12-13. Also see the Hong et al. patent's listing of sorbose as an exemplary ketohexose at column 5 line 47.

another due to their known similarity in physical properties.

17. Therefore, one of ordinary skill in the art in 1989 would have presumed that the disclosure of use of sorbose as a useful carrier material indicated with a high degree of likelyhood that the other ketohexoses were also useful carrier materials.

18. Thus, I believe that the disclosure of sorbose as a useful carrier material would have conveyed to one of ordinary skill in the art in 1989 that Mr. Hatley and myself (i.e, the named inventors of the patent) understood that sorbose or any of its isomers would make a useful carrier material.

19. Subsequent to 1989, I realized that certain ketohexoses were not useful for the invention, and that the glass transition temperature had no relation to melting points. However, in 1989, those facts were unknown to me and to the others skilled in the art.

D. **Claims 55 and 56**

20. Counsel informs me that claims 55 and 56 now read:

> 55. (Not Amended) The composition according to claim 17 wherein said carrier substance comprises condensation products of sugars with alcohols.
>
> 56. (Once Amended) The composition according to claim 17 wherein said carrier material comprises sugar alcohols.

21. Sugar alcohols are always linear chain molecules. They can be either mono or poly saccharides.

22. The melting point of sugar alcohols were well known to one of ordinary skill in

the art in 1989.

23. One of ordinary skill in the art was informed by column 13 in the specification that the exemplary sugar alcohols were suitable carrier materials for the storage stabilizing unstable materials.

24. Moreover, one of ordinary skill in the art in 1989 would have drawn the inference, based upon the known similarities in melting point and other physical properties, that all sugar alcohols were likely to be suitable as carrier materials for the claimed invention. Again, this was due to the similarity in known values for physical properties of that class of materials, coupled with my inventive general concept of evaporative drying all the way to the glassy state. I now know that the inference would have been incorrect insofar as mannitol is concerned, because it alone of all the isomeric hexitols crystallizes from solution.

E. **Claim 67**

25. Counsel informs me that claim 67 now reads:

> 67. (Once Amended) The composition according to claim 17 wherein said purified biologically active [substance] material is a dehydrogenase.

26. This application teaches stabilizing enzymes that are unstable in aqueous solution. The specification contains a section entitled "MATERIALS STORED" the second paragraph of which specifically refers to proteins, and more specifically to enzymes. In fact, the third paragraph of that section indicates that enzyme substrates are in general materials to which the disclosed invention may be applied. Specification column 3 lines 8-13.

27. Furthermore, it was well known in the art in 1989 that "[f]ew enzymes are inherently stable in solution." Page 1 line 3 in the WO 90/05182 reference, which counsel informs me is cited as reference AP and was considered by the examiner June 29, 1999. It was well known in 1989 that dehydrogenases are enzymes.

28. In addition, it was well known in the art in 1990 that dehydrogenases, as a class, were unstable in aqueous solution.

29. Examples 1, 2, 5, 7, 9, 11, 12, and 13 in the specification all disclose storage of dehydrogenases.

30. One of ordinary skill in the art in 1989 reading the specification would have realized from the fact that the majority of the examples were examples of storage of dehydrogenases and that dehydgrogenases were known to be storage unstable that the inventors contemplated their invention to be generally applicable to stabilize dehydrogenases.

F. **Claims 68, 71, and 72**

31. It was well known to one of ordinary skill in the art in 1989 that restriction, oxidase, and reductase enzymes were all unstable in aqueous solutions. These materials were unstable in the sense that they would deteriorate during any practical freeze drying process. Our invention and patent provided the first means known to stabilize at room temperature restriction enzymes in the solid state. In fact, [redacted] took a license for this invention specifically so it could stabilize restriction enzymes at room temperature.

32. This application teaches that unstable materials, such as enzymes, are stabilized

by formation of the glassy state, and that exemplary restriction, reductase, and oxidase enzymes are stabilized in the glassy state. Therefore, one of ordinary skill in the art would have understood that the disclosure in the application of any one of a restriction, reductase, or oxidase enzyme used as an example of the invention indicated that the inventors contemplated stabilizing all such enzymes, since they all shared the instability problem. Accordingly, the examples in this application showing that the invention is applicable to restriction, reductase, and oxidase enzymes indicates that the inventors believed that the invention to be applicable to those classes of enzymes generally, and not just to the specific examples used in the specification.

G. **Claims 73 and 80**

33. This application discloses that the goal of my invention was to store the active materials, not to store the carrier substance. Moreover, column 10 line 1 discloses a carrier to protein ratio of 2 to 1, column 11 line 8 discloses a carrier to protein ratio of 1 to 1, and column 12 line 21 discloses a carrier to enzyme ratio of 1 to 1. Accordingly, in view of the examples disclosing the concentration ratios mentioned above, one of ordinary skill in the art reading the application in 1990 would have understood that we the inventors intended to store relatively high concentrations of active material.

34. The fact that the disclosure taught one of ordinary skill in the art storing high concentrations of the active materials, and the fact that the specification specifically discloses a ratio of 2 to 1, shows that the we specifically considered the 2 to 1 ratio within the scope of our invention.

H. **Claim 75**

35. Example 1 discloses a dissolution pH of 7.0. See column 7 line 48-52, which state that:

> About 50% was placed into a dry mortar and 0.2 ml of a solution containing 1,000 units/ml lactate dehydrogenase LDH (ex rabbit muscle) and 0.01 M phosphate buffer pH 7.0 was added and mixed well into the Ficoll.

36. In addition, example 5 discloses by reference to example 1, the same dissolution pH as example 1. Furthermore, examples 7, 8, 9, and 10 disclose the same dissolution pH as examples 1, by reference to example 5, and hence, to example 1. Thus, there is disclosure in the application indicating that we the inventors considered a dissolution pH of about 7 to be within the scope of our invention.

I. **Claims 96 and 103**

37. Claims 96 and 103 recite an upper temperature limit of 150°C, and that upper limit is disclosed in the application.

38. The disclosure in the specification of temperature limits, particularly at column 4 line 12-15, would have taught one reading the specification in 1990 that we the inventors contemplated drying at temperatures up to 150°C.

III. Facts Relating the Rejections of Claims as Obvious Based Upon the Koyama et al. Patent and the Prior Art

39. It would not have been obvious to one of ordinary skill in the art in 1989 to form

the dried compositions of the Koyama et al. patent using "conventional drying procedures" at reduced pressure and at a temperature below 30°C. Moreover, in 1989, there were no non-freeze drying "conventional drying procedures carried out at a reduced pressure and temperature below 30 °C" (quoting the Koyama et al. patent column 2 lines 52-54) used on proteinaceous bioactive compounds. In fact, Koyama et al. does not even show that drying without freezing unstable bioactive compounds was feasible. Hence, one of ordinary skill in the art in 1989 reading the Koyama et al. patent would have recognized the reference to non-freeze drying as mere surplusage unsupported by any experimental results and therefore would not have been motivated to dry without freeze drying. One reason that one of ordinary skill in the art in 1989 would not have been motivated to dry without freezing was that one of ordinary skill in the art would have believed that drying purified biologically active samples without first freezing them would destroy unacceptably large fraction of their activity. In fact, it was widely if not universally believed in the art in 1989 that freeze drying was the least harmful way of drying biologically active materials. For example, see page 3 right hand column of "Good Pharmaceutical Freeze Drying Practice," which indicates that even in 1997 freeze drying was still considered by many to be the least harmful way to freeze dry biologically active or unstable materials, and that was also certainly the case in 1989.[4] My teaching in my patent, which is that acceptable results could be obtained without freeze drying, ran counter to the accepted understanding in the art in 1989.

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[4]Attachment 35 Title page, copyright page, contents pages, and page 5 of "Good Pharmaceutical Freeze-Drying Practices," Interpham Press, Inc. (1997).

40. Even assuming for the sake of argument one of ordinary skill in the art in 1989 was in fact motivated to dry an aqueous unstable material without freeze drying, there was no teaching suggesting using the degree of drying required to obtain a composition that is in a glassy state when existing at 20° C. Because those skilled in the art did not know that the amount of residual water was significant, it is possible that following Koyama et al.'s suggestion to experiment with non-freeze drying would not have resulted in a glassy state material. I note, for example, that Koyama et al. also suggests including mineral buffers or saccharides. I know that mineral buffers, which Koyama et al. teaches to be desirable, depress the Tg. The point here is that nobody realized at the time of my invention that the glassy state was significant, and therefore nobody realized either (1) the degree of drying needed to reach the glassy state or (2) what additives would prevent the glassy state from existing at 20° C. Hence, there is no guarantee that acting on Koyama et al.'s vague suggestion to use "conventional" drying would have resulted in a material in a glassy state at 20° C.

IV. **Jurat**

41. I swear under penalty of perjury of the laws of the United States that the foregoing is true and correct.

October 2, 2000
DATE

F. Franks
FELIX FRANKS

Printed: September 26, 2000 (4: 1PM)
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NEW DOCKET NO. INHA0012ICO/US (OLD DOCKET NO. 212345US22CONT)

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:
FELIX FRANKS ET AL : EXAMINER: RUSSEL

SERIAL NO. 09/939,689

FILED: AUGUST 28, 2001 : GROUP ART UNIT: 1653

FOR: STORAGE OF MATERIALS

ASSENT OF THE ASSIGNEE UNDER 37 C.F.R. §1.172

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Inhale Therapeutic, Systems Inc., the assignee of the entire right, title and interest, based on my review of the papers assigning said interest, does hereby assent to the above-captioned reissue application. I have full authority to give such assent.

All statements made herein of my knowledge and true and all statements made on information and belief are believed true. I am aware that willful false statements and the like are punishable by fine, imprisonment, or both pursuant to 18 USC 1001, and that such willful false statements may jeopardize the validity of U.S. Patent 5,098,893, the above-captioned reissue application, and patent issuing thereon.

CERTIFICATION UNDER 37 C.F.R. 3.73(b)

I, the undersigned, certify that I am an individual empowered to act on behalf of Inhale Therapeutic Systems, Inc., the assignee of the entire right, title and interest of the above-captioned application by virtue of an assignment of said application.

I further certify that I have reviewed all the documents in the chain of title of the patent application identified above, that the assignment has been recorded in the U.S. Patent and Trademark Office at reel no. 8783, frame 0704, that I have reviewed the assignment recorded at said reel and frame, and that to the best of knowledge and belief title is in the above-noted assignee.

I further declare that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine, imprisonment, or both pursuant to 18 USC 1001, and that such willful false statements may jeopardize the validity of the above-captioned Reissue Application, and any patent issuing thereon.

October 3, 2002

Felissa H. Cagan

Felissa H. Cagan

Senior Director, Intellectual Property
Inhale Therapeutic Systems, Inc.